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REACTIONS OF CYTOTOXIC NOR-DITERPENOID DILACTONES IN PODOCARPUS NAGI: MODIFICATIONS OF RING A FUNCTIONAL GROUPS

Yuji HAYASHI*, Takeshi MATSUMOTO*, Toshiaki HYONO*, and Takeo SAKAN**

* Faculty of Science, Osaka City University, Sugimotocho, Sumiyoshiku, Osaka 558

** The Institute of Food Chemistry, Shimamotocho, Mishimagun, Osaka 618

Chemical modifications of the ring A functional groups on the biologically active nor-diterpenoid dilactones of Podocarpus plants are described. Some results obtained here are different from the reported unusual properties of these unique compounds.

Some anomalies have been experienced on the reactivity of nor-diterpenoid dilactones of Podocarpus plants[1]. The dilactones constitute an important group of plant components with a wide variety of biological activities, e.g., anti-tumor activity[2], plant growth regulation[3a,c,12a], and toxicity for insect larvae[5]. In order to correlate the dilactones chemically, we have investigated thier reactivities towards various types of reagents. This paper deals with the modifications of ring A functional groups, some of which oppose the reported behavior of the lactones[4]. The derivatives presented here are also important for correlation of other new analogues and determination of the structure-activity relationships on the biological activities.

Nagilactone E[3a] (1), the most abundant component (ca. 0.1% from fresh material) in the root bark of Podocarpus nagi Zoll. et Moritzi, was treated with $POCl_3$ in pyridine at room temperature to give quantitatively a phosphate ester (2), mp 207°, ν_{max}^{KBr} 1783, 1700 cm^{-1}, which was characterized as a dimethyl ester (3) (CH_2N_2), mp 225°, $C_{21}H_{29}O_9P$, ν_{max}^{KBr} 1778, 1703, 1055~1035 cm^{-1}, m/e(20 eV) 456(M^+, 11), 441(47), 413(13), 330(36), 315(38), 287(32), 271(15), 259(18), 243(19), 229(12), 215(14). When 2 was refluxed in pyridine, an expected elimination reaction was completed in 7 h. A dehydration product (4)[10] obtained, mp 236°(sublime), $C_{19}H_{22}O_5$, λ_{max}^{EtOH} 219 nm (ε;10900), ν_{max}^{KBr} 1765, 1700 cm^{-1}, m/e(20 eV) 330(M^+, 2), 287(17), 271(24), 259

(14), 243(24), 229(35), 215(37), 199(37), was identified with podolide[2b], a cytotoxic principle of Podocarpus glacilior. In the product (4), irradiation of the allylic methylene protons at 2.05 ppm (H-1) exhibits 23% of NOE on H-11 signal, which indicates the 2,3-double bond.

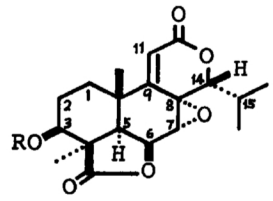
In contrast to the reported poor reactivity on epoxidation[4], the 2,3-double bond of 4 reacted, slowly but definitely, with m-chloroperbenzoic acid in the presence of a radical inhibitor[9] (in $CHCl_3$, 60°, 40 h). An epoxide (6) was formed in an acceptable yield as a sole product, mp 275°(sublime), $C_{19}H_{22}O_6$, λ_{max}^{EtOH} 218 nm (ε:9800), ν_{max}^{KBr} 1770, 1705 cm^{-1}, m/e(20 eV) 346(M^+, 7), 318(12), 303(74), 275(68), 247(38), 229(36), 215(21), 203(29). Based on the pmr parameters of the H-1, H-2, and H-3, the configuration of the epoxide ring of 6 was assigned as 2α, 3α-orientation, which is epimeric to a natural dilactone (8)[6,8]. An analogous result was obtained from oxidation of 16-hydroxypodolide (5)[6] to give an epoxide (7), mp 272°(dec), $C_{19}H_{22}O_7$, ν_{max}^{KBr} 3540, 1777, 1700 cm^{-1}, m/e(20 eV) 362(M^+, 16), 347(16), 332(24), 305(100), isomeric to sellowin A (9)[4b,c]. Thus, the ring A double bond was found to be chemically more reactive at less hindered α-side. Attempts to prepare the 2β,3β-epoxide from 4 and 5 were unsuccessful.

Brown and Sanchez L. have reported the unusual reductive deoxygenation[4b] of a 1β,2β-epoxy-3β-hydroxy system with chromous chloride to form a 1,2-saturated-3β-hydroxy system. By this reaction, nagilactone C (10)[3b] has directly been transformed to sellowin C (14). However, the chromous ion catalyzed deoxygenation of the nagilactone under the following conditions produced a 1,2-unsaturated analogue (11). The reaction was conducted at 30° for 4 h in DMF under pure nitrogen. Use of five equivalents of the chromous perchlorate-ethylene diamine complex[7] gave 11 in highest yield. The product (52%) was almost pure 11 without purification, and no 1,2-saturated analogue was detected. The compound (11), mp 287~9°, $C_{19}H_{22}O_6$, λ_{max}^{EtOH} 300 nm, ν_{max}^{Nujol} 3500~3300, 1750, 1695, 1630, 1550 cm^{-1}, exhibits two olefinic proton signals at 6.89(d, J = 9.5 Hz, H-1) and 6.17(dd, J=6.0, 9.5 Hz, H-2) ppm, which appear in the modified AB type[11]. About 30% of NOE between the H-1 and the H-11 was determined with a diacetate (12) (Ac_2O-pyridine), mp 248°, ν_{max}^{Nujol} 1780, 1740, 1720, 1630, 1545 cm^{-1}. The olefinic alcohol (11) underwent hydrogenolysis (5%-Pd-C/EtOH/$HClO_4$) at C-3 with the concomitant double bond migration, and yielded an olefin (13), mp 290°(sublime), $C_{19}H_{22}O_5$, ν_{max}^{Nujol} 3440, 1760, 1695, 1635, 1550 cm^{-1}. On the pmr, 13 gave a broad three-proton singlet[11] at

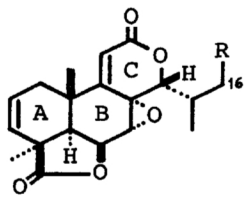
Table 1. The pmr parameters of the lactones (pyridine-d_5)

Lactones	H^1	H^2	H^3	H^5	H^6	H^7	H^{11}	H^{14}	H^{15}	CH_3*	CH_3**
3‡‡	--	--	4.70 br m	2.06 d (4.0)	5.18 dd (1.5, 4.0)	4.26 d (1.5)	6.22 s	4.62 d (4.0)	--	1.27 1.60	1.04 (7.0) 1.18 (7.0)
4	2.05 br d (~3.0)	5.80 dt (3.0, 3.0, 10.0)	5.90 d (10.0)	2.07 d (5.0)	5.16 dd (1.5, 5.0)	4.24 d (1.5)	6.17 s	4.61 d (4.0)	--	1.16 1.30	1.05 (7.0) 1.18 (7.0)
6	***	3.37 m	3.52 d (4.0)	1.86 d (5.0)	5.11 dd (1.5, 5.0)	4.20 d (1.5)	6.07 s	4.53 d (4.0)	--	1.11 1.45	1.01 (7.0) 1.13 (7.0)
7†	****	3.38 m	3.52 d (3.5)	1.86 d (5.0)	5.12 dd (1.5, 5.0)	4.33 d (1.5)	6.16 s	4.82 d (5.0)	--	1.13 1.46	1.30 (7.0)
11	6.89 d (9.5)	6.17 dd (6.0, 9.5)	4.53 d (6.0)	2.17 d (6.0)	5.02 dd (6.0, 8.5)	5.63 d (8.5)	6.58 s		3.48 m (6.5)	1.41 1.98	1.21 (6.5) 1.29 (6.5)
12#	6.80 d (9.8)	5.88 dd (6.0, 9.8)	5.56 d (6.0)	2.23 d (6.0)	4.96 dd (6.0, 9.1)	6.36 d (9.1)	6.22 s		3.00 m (6.8)	1.55 1.55	1.24 (6.8) 1.26 (6.8)
13#	2.14 br d (~3.0)	5.88 br s	5.88 br s	2.00 d (5.5)	4.95 dd (5.5, 9.0)	5.30 d (9.0)	5.88 s		3.24 m (6.5)	1.38 1.38	1.25 (6.5) 1.34 (6.5)

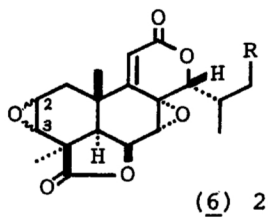
* singlet methyl signals. ** doublet methyl signals. *** $H^{1\alpha}$: 1.59 dd (1.5, 14.0), $H^{1\beta}$: 2.14 dd (6.5, 14.0). **** $H^{1\alpha}$: 1.58 dd (1.5, 14.0), $H^{1\beta}$: 2.12 dd (6.0, 14.0). † H^{16}: 4.00 dd (7.0, 10.5), 4.11 dd (4.0, 10.5). ‡‡ methoxyl signals: 3.84 d (11.5), 3.90 d (11.5). # $CDCl_3$ as solvent.



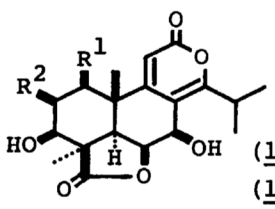
(1) R=H
(2) R= $PO(OH)_2$
(3) R= $PO(OCH_3)_2$



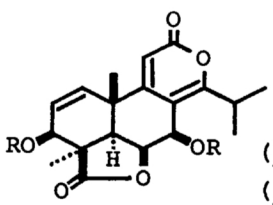
(4) R=H
(5) R=OH



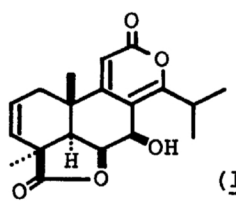
(6) 2α,3α-epoxy, R=H
(7) 2α,3α-epoxy, R=OH
(8) 2β,3β-epoxy, R=H
(9) 2β,3β-epoxy, R=OH



(10) R^1,R^2= >O
(14) R^1=R^2=H



(11) R=H
(12) R=Ac



(13)

5.88 ppm due to the olefinic protons, H-2, H-3, and H-11, analogously to podolide (4) and 16-hydroxypodolide (5). Presumably, the 2,3- rather than the 1,2-position is sterically more favorable for the ring A double bond. Selective hydrogenation of the double bond at either the 1,2- or 2,3-position was unsuccessful, because of occurrence of undesired transformations, the saturation of the ring C double bond (PtO_2)[3a,b] and the reductive cleavage of the 7α,8α-epoxide group (Pd-C)[12].

Notes and References

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8. The corresponding β-epoxide of the natural dilactones[4c,6] shows the following coupling constants: $J_{1\alpha,2\alpha}$= 1.5, $J_{1\beta,2\alpha}$= 2.0, $J_{1\alpha,1\beta}$=14.5, $J_{2\alpha,3\alpha}$= 4.0 Hz.
9. Y.Kishi, A.Aratani, and T.Goto, Chem. Commun., 1972, 65: 4,4'-Thiobis(6-t-butyl-m-cresol) was used as a radical inhibitor.
10. All spectral data of 4 are well consistent to the reported structure of podolide. Unfortunately, the direct ir or pmr comparison was not possible, since good spectral data of natural podolide were not available.
11. In the 1,2-unsaturated compounds, the H-1 is more strongly affected than the H-2 by the α-pyrone ring, appearing at unusually low field (6.89 ppm), while the 2,3-unsaturated ones, e.g., 4, 5, and 13, show almost overlapped olefinic proton signals: 4 ($CDCl_3$): 5.88(br s, H-2 and H-3), 6.00(s, H-11) ppm, 5 ($CDCl_3$): 5.92(br s, H-2 and H-3), 6.04(s, H-11) ppm.
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